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(54) Title of the Invention p-Toluene Sulfonate for Water-Soluble Quinolone Derivative

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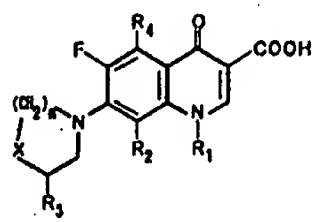
Specification

1. Title of the Invention p-Toluene Sulfonate for Water-Soluble Quinolone Derivative

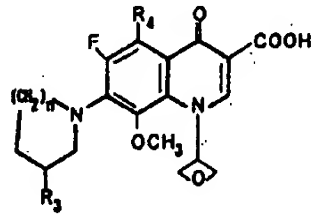
2. Scope of Patent Claim



..... (I)

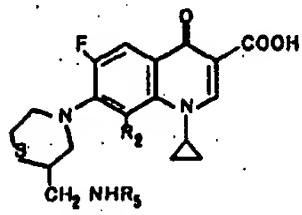
1. A p-toluene sulfonate compound which is represented by the following general formula (I): . (where R_1 is a cyclopropyl group or an oxetanyl group; R_2 is a fluorine atom or a methoxy group; R_3 is an amino group, an aminomethyl group or a methyl aminomethyl group; X is a carbon atom or a sulfur atom; R_4 is a hydrogen atom or an amino group; and n is 1 or 2);

2. The composition of Claim 1 where the compound indicated in the aforementioned general formula (I) is represented by the following general formula (II):



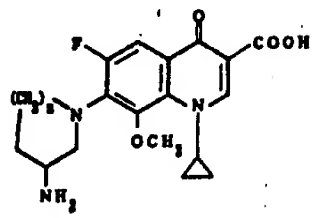
(where R_3, R_4 and n are the same as indicated previously);

3. The composition of Claim 1 wherein the compound indicated in the aforementioned general formula (I) is represented by the following general formula (III):



(where R_5 is a hydrogen atom or a methyl group and R_2 is the same as indicated previously);

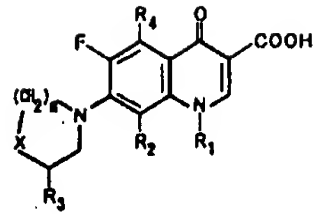
4. The composition of Claim 1 wherein the compound represented in the aforementioned general formula (I) is represented by the following general formula (IV):



(where n is the same as indicated previously).

3. **Detailed Description of the Invention**
(Industrial Application)

The present invention relates to a p-toluene sulfonate for a quinolone group antimicrobial agent. The present invention relates particularly to a p-toluene sulfonate for a quinolone group antimicrobial agent indicated in the following general formula (I):



(I)

(where R_1 is a cyclopropyl group or an oxetanyl group; R_2 is a fluorine atom or a methoxy group; R_3 is an amino group, an aminomethyl group or a methyl aminomethyl group; X is a carbon atom or a sulfur atom; R_4 is a hydrogen atom or an amino group; and n is 1 or 2).

The compound in the present invention is highly safe, has a strong antibacterial action and is a substance which is useful as a medicine.

(Description of the Prior Art / Problems Which the Present Invention is Intended to Resolve)

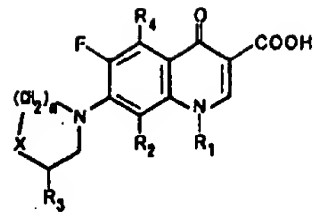
Quinolone group antibacterial agents are widely used and do not exhibit a cross tolerance with antibacterial agents in other systems. As a result, a variety of compounds—including those currently available on the market—are in use. However, the only drawback in their antibacterial activity is that it is insufficient relative to the streptococcus genus and enterococcus genus. In addition, many of the antibacterial agents in this system are problematical in that side-effects in the nervous system develop and the agents require extreme caution when used.

The water-soluble quinolone group antibacterial agent in the present invention which is indicated by the general formula (I) is characteristic in that its antibacterial activity relative to the staphilococcus genus, streptococcus genus and enterococcus genus is much stronger than that of pre-existing quinolone group antibacterial agents. However, since it is highly water-soluble, side-effects brought on by excess absorption when an overdosage was administered orally were problematical.

The inventors took this situation into consideration and after a great deal of hard work and research on a method of regulating the absorption of a water-soluble quinolone group antibacterial agent when administered orally, found that the p-toluene sulfonate compound in the present invention indicated by the aforementioned general formula (I) has a stronger antibacterial activity relative to the streptococcus genus and other Gram-positive bacteria than that of the commonly known quinolone group antibacterial agents ofloxacin, norfloxacin, ciproloxacin and enoxacin, that there is little excess absorption when an overdosage is administered orally and is highly safe, and they arrived at the present invention.

(Means Used to Resolve the Problems)

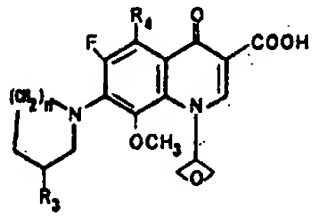
The present invention provides a p-toluene sulfonate compound which is represented by the following general formula (I):



..... (I)

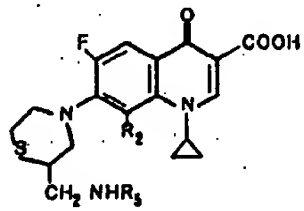
(where R_1 is a cyclopropyl group or an oxetanyl group; R_2 is a fluorine atom or a methoxy group; R_3 is an amino group, an aminomethyl group or a methyl aminomethyl group; X is a carbon atom or a sulfur atom; R_4 is a hydrogen atom or an amino group; and n is 1 or 2).

The groups of compounds indicated by the following general formulas (II) through (IV) are especially suitable for the compound in the present invention which is indicated by the general formula (I):



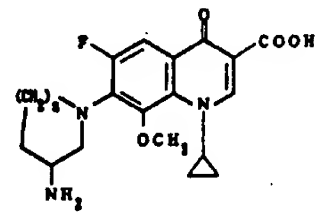
..... (II)

(where R_3, R_4 and n are the same as indicated previously);



..... (III)

(where R_5 is a hydrogen atom or a methyl group and R_2 is the same as indicated previously);



..... (IV)

(where n is the same as indicated previously).

The following are all specific examples of the p-toluene sulfonate in the groups of compounds indicated in the aforementioned general formulas (II) through (IV).

7-(3-aminopiperidine-1-yl)-6-fluoro-8-methoxy-1-(3-oxetanyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate.....(1),

7-(3-aminopyrrolidine-1-yl)-5-amino-6-fluoro-8-methoxy-1-(3-oxetanyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate.... .....(2),

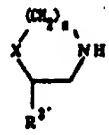
7-(2-aminomethyl thiomorpholine-4-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate.....(3),

1-cyclopropyl-6-fluoro-7-(2-methyl aminomethyl thiomorpholine-4-yl)-8-methoxy -1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate.....(4),

7-(3-aminopyrrolidine-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate.....(5),

7-(3-aminopiperidine-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate.....(6).

The compound in the present invention which is indicated by the general formula (I) are manufactured as follows. The compound which is indicated by the following general formula (V):



..... (V)

(where X and n are the same as indicated previously; and R^3 is the same as indicated previously or when R^3 is a group which contains an amino group, that amino group indicates a group which is substituted by a lower alcohol alkanoyl group) are reacted with commonly known compounds such as 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate, 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4—dihydro-4-oxoquinoline-3-carboxylate and other 6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline derivatives or lower alcohol alkyl esters of compounds of these, hydrolysis is carried out as needed so that the compound indicated by the general formula (I) in which the eighth position is a fluorine atom is manufactured. Next, we were able to manufacture the compound in the present invention indicated by the general formula (I) in which the eighth position is a methoxy group by reacting this with sodium methoxide.

The compound in the present invention indicated by the general formula (I) which was manufactured in this way was made into the p-toluene sulfonate using the regular method. Tosylation was carried out by dissolving the compound indicated in the corresponding general formula (I) in a mixed solution of water and methanol and then adding an equimolar amount of p-toluene sulfonate. Isolation of the desired p-toluene sulfonate from the reaction solution was carried out by concentrating the reaction solution at reduced pressure and by filtering out the crystals which were precipitated.

(Practical Embodiments of the Present Invention)

Next, we shall explain the present invention using experimental embodiments and practical embodiments of it.

Experimental Embodiment 1

Results of comparing the antibacterial activity of the compound in the present invention with commonly known quinolone group antibacterial agents ofloxacin and norfloxacin are indicated in Table 1. Further, the numbers of the compounds in Table 1 correspond to the numbers of the compounds used previously.

1... 7-(3-aminopiperidine-1-yl)-6-fluoro-8-methoxy-1-(3-oxetanyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate,

2... 7-(3-aminopyrroridine-1-yl)-5-amino-6-fluoro-8-methoxy-1-(3-oxetanyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate,

3...7-(2-aminomethyl thiomorpholine-4-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate,

4...1-cyclopropyl-6-fluoro-7-(2-methyl aminomethyl thiomorpholine-4-yl)-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate.

Table 1

Name of Bacterium	Compound being Studied	Compound in Present Invention			
		(1)	(2)	(3)	(4)
Gram (+)	Staphilococcus aureus 209P JC - 1	0.20	0.78	0.024	0.01
	Streptococcus pneumoniae No. 28n	1.56	3.13	0.78	0.3
	Enterococcus fecalis No. 14	1.56	3.13	0.39	0.3
(Gram (-)	Escherichia coli NIHJ JC - 2	0.10	0.20	0.10	0.2
	Klebsiella pneumoniae No. 42	0.10	0.3	0.10	0.2
	Proteus vulgaris No. 33	0.20	0.20	0.39	0.2
	Citrobacter Freundi No. 7	1.56	1.56	1.56	0.7
	Enterobacter cloacae NeK – 39	0.20	0.78	0.39	0.3
	Pseudomonas erginasa AK 109	0.78	0.78	1.56	1.5

Note) OFLX: ofloxacin; NFLX: norfloxacin

Experimental Embodiment 2 **Maximal Concentration in Blood of Mice (Cmax : μg / ml)**

We administered a water suspension of compound (5) (p-toluene sulfonate) in the invention mentioned previously to eight-week old DDY strain male mice in 80 mg/kg, 200 [sic] mg/kg and 3000 mg/kg doses using a special oral probe for mice. 15 minutes after the suspension had been administered, the mice were decapitated and blood was collected using the regular method. After blood serum dialysis had been carried out, it was submitted for bioassay using bacillus subtilis (ATCC 6633). We used a technical product of the compound in the present invention as a control. As a result, the compound in the present invention (p-toluene sulfonate) exhibited approximately 70 % concentration in the blood when administered in a 80 mg/kg dose compared to when the technical product was administered. It exhibited a concentration in the blood of approximately 20 % when administered in doses of 2000 [sic] mg/kg and 3000 mg/kg. These results confirmed the fact that the safety of the compound in the present invention relative to an overdosage was high.

Practical Embodiment 1

We dissolved the 7-(3-aminopiperidine-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylate (melting point of 176 to 177°C) in a methanol : water (3:1) solution and added a solution made by dissolving p-toluene sulfonate • H_2O in water. We concentrated the reaction solution under reduced pressure halfway and cooled it. We filtered out the crystal which had been precipitated. When we recrystallized this from the methanol—water, we obtained colorless needle crystals with a melting point of 235 to 40 [sic]°C. [Translator's note: most likely "240°C" is intended].

Practical Embodiment 2

We obtained 7-(3-aminopyrrolidine-1-yl)-6-fluoro-8-methoxy-1-cyclopropyl-1,4-dihydro-4-oxoquinoline-3-carboxylate p-toluene sulfonate (melting point of 268 to 270°C, recrystallized from methanol—water) by carrying out Practical Embodiment 1 as we did previously. The solubility of this (4.5 mg/ml, 0.1 N • HCl water) was approximately 1/10 of the solubility of the hydrochloride which had been manufactured as a control.

(Effect of Invention)

The p-toluene sulfonate compound in the present invention which is indicated by the aforementioned general formula (I) is effective in that it had a stronger antibacterial activity relative to the streptococcus genus and other Gram-positive bacteria than the commonly known quinolone group antibacterial agents, had little excess absorption when an overdosage was administered and was extremely safe.

Patent Applicant: Takeshi Yokota

Patent Agent: Patent Attorney Tetsuya Nozaki